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INVITED ARTICLE

A new reportable disease is born: Taiwan Centers for Disease Control's response to emerging Zika virus infection

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Zika virus infection, usually a mild disease transmitted through the bite of Aedes mosquitos, has been reported to be possibly associated with microcephaly and neurologic complications. Taiwan's first imported case of Zika virus infection was found through fever screening at airport entry in January 2016. No virus was isolated from patient's blood taken during acute illness; however, PCR products showed that the virus was of Asian lineage closely related to virus from Cambodia. To prevent Zika virus from spreading in Taiwan, the Taiwan Centers for Disease Control has strengthened efforts in quarantine and surveillance, increased Zika virus infection diagnostic capacity, implemented healthcare system preparedness plans, and enhanced vector control program through community mobilization and education. Besides the first imported case, no additional cases of Zika virus infection have been identified. Furthermore, no significant increase in the number of microcephaly or Guillain- Barré Syndrome has been observed in Taiwan. To date, there have been no autochthonous transmissions of Zika virus infection.

In the nearly seven decades following the isolation of Zika virus from a rhesus monkey caged in Zika Forest of Uganda, Zika virus had quietly made its way across Asia and the South Pacific.[1] Exposure to Zika virus causes no symptoms in about 80% of those infected.[2] For persons who become symptomatic, they typically present with rash and fever, accompanied by arthralgia, arthritis, or non-purulent conjunctivitis.[2] In 2015, an increase of babies born with microcephaly in Brazil temporally associated with Zika virus infection in mothers raised the possibility that Zika virus infection might cause microcephaly.[3] Furthermore, some Brazilian states affected by Zika virus infections have reported an increase in Guillain- Barré Syndrome (GBS) during January to November 2015, compared to 2014.[4] The

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clustering of microcephaly and neurologic complications lead the World Health Organization (WHO) to declare the situation a public health emergency of international concern (PHEIC).[5]

We report the laboratory findings of the first imported case of Zika virus infection, its implications, and the government's response.

Case report

On January 10, 2016, a Thai national entering Taiwan Taoyuan International Airport was found to have fever by quarantine officers. The person, aged 24 years, reported to have fever and headache starting the day prior to his arrival in Taiwan. He had history of dengue fever, and had not traveled out of Thailand during the three months prior to his arrival in Taiwan. Although blood taken at the airport was dengue virus NS-1 negative, it was sent to the laboratory of the Taiwan Centers for Disease Control (Taiwan CDC) to conduct real-time RT-PCR tests for suspected arboviral infections. Routine screening process used two samples for real-time RT-PCR: first with specific primers for dengue virus types 1 to 4 and severe fever with thrombocytopenia syndrome (SFTS), and second with flavivirus consensus primers and chikungunya virus specific primers. PCR products were found in the second sample. Resultant PCR products were sequenced and found to be Zika virus. The patient's blood sample was also tested for flavivirus antibodies using capture IgM/IgG ELISA. Blood was taken on day 2 and day 13 after disease onset. Testing blood taken on day 2 of disease onset, anti-Zika IgG and IgM was undetectable, but was positive for anti-dengue IgG and anti-Japanese encephalitis IgG. Testing blood taken on day 6 of disease onset, anti-Zika IgM and IgG remained undetectable, but was positive for anti-dengue IgM and IgG, and anti-Japanese encephalitis IgM and IgG. No virus was isolated. After entry into the country, the patient became afebrile, and recovered fully. Two other travelers traveling with him were his coworkers who also resided in northern Thailand; they both tested negative for Zika virus and dengue virus infections.

Analysis of Zika virus gene sequence found from this Thailand imported case indicated that the virus belonged to the Asian lineage and is closely related to virus from Cambodia (Figure 1).

Discussion

Zika virus, like dengue virus, is mainly spread from person to person through the bite of *Aedes* mosquitos, which are present throughout Taiwan. In 2014 and 2015, there have been unprecedented large outbreaks of dengue fever.[6] However, this is the first confirmed Zika virus infection case detected among the 50,000 samples collected through the Taiwan CDC arbovirus infection screening program which began in 2003. This event raised the awareness of possible importation and spread of Zika virus in Taiwan.

In response to increased threat of Zika virus importation and spread, it has been found that during 2010—2014, an average of 1.47 microcephaly cases/100,000 births (all births) were reported (range 1.19—1.69/100,000) to the Taiwan Birth Registry of the Health Promotion Administration. Possible association between microcephaly and Zika virus infection was first reported from Brazil in November 2015, because both conditions were reported in highest numbers in northeastern Brazil, and two mothers who gave birth to infants with microcephaly were confirmed to be infected by Zika virus.[3] Case reports indicating Zika virus found in amniotic fluids taken from women whose fetuses were diagnosed with microcephaly by ultrasound further strengthen the association between Zika virus infection and microcephaly.[7] Epidemiological studies are ongoing to ascertain the strength of association between microcephaly and Zika virus infection.

Another possible complication associated with Zika virus infection is Guillain-Barré Syndrome. Although an association was reported during the outbreak in French Polynesia,[8]

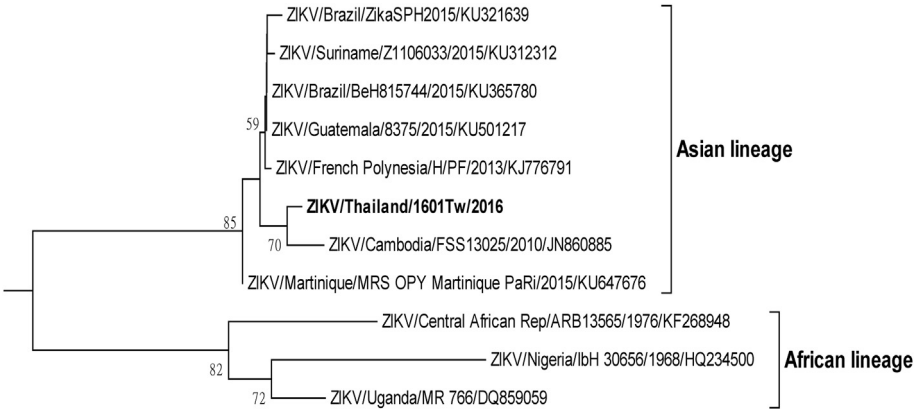

Figure 1 Phylogenetic relationship of Zika virus (ZIKV) sequence from an imported case of ZIKV infection, Taiwan, 2016. The tree was constructed on the basis of nucleotide sequence of capsid and partial premembrane protein (C-preM) genes (653 bp; nt positions 1-653 of the prototype MR 766 genomic sequence, GenBank accession number DQ859059) of 11 ZIKV strains. Sequence obtained in this study is indicated in **boldface**. Viruses were identified by using the nomenclature of virus/country/strain/year of isolation/GenBank accession number. Analysis was performed by using MEGA 6 software and neighbor-joining method. Bootstrap support values $>$ 50 are shown (1,000 replicates). Spondweni virus sequence was used as the outgroup virus.

the association has not been clearly demonstrated in Brazil. Some, not all, states in Brazil with Zika virus spread reported an increase in Guillain- Barré Syndrome; however, others reported a decrease.[3] According to the Taiwan National Health Insurance records, cases with diagnosis of Guillain- Barré Syndrome remained stable in the past 5 years, with an average of 1.48 cases/100,000 population diagnosed each year (range: 1.29—1.55/100,000).

To detect Zika virus, as an island nation, Taiwan CDC has been testing suspected imported dengue fever patient blood samples using flavivirus consensus primers for the identification of multiple flaviviruses, including Zika virus, since 2003. This allowed us to identify the first case of Zika virus infection imported from Thailand, though the antibody tests did not show positive findings. The interpretation of Zika virus antibody may be complicated by cross-reactivity with other flaviviruses.[9,10] As demonstrated in our case, even though the patient had proven Zika virus infection by RT-PCR, capture ELISA for dengue and Japanese encephalitis IgM/IgG was positive, probably because of previous infections or vaccinations. Taiwan provides routine immunization against Japanese encephalitis and has had large outbreaks of dengue fever; both will make confirmation of Zika virus infection by serology difficult, when virus could not be isolated or viral sequences found.

On January 22, 2016, Taiwan CDC listed Zika virus infection as a Category 2 reportable disease. As WHO declared a Public Health Emergency of International Concern (PHEIC) because of the clustering of microcephaly and neurologic disorders on February 1, 2016,[5] Taiwan CDC changed Zika virus infection listing to be a Category 5 reportable disease. Physicians should report all suspected cases to Taiwan CDC within 24 hours. Furthermore, the Central Epidemic Command Center (CECC) was activated on February 3 for the monitoring and coordination of the emergency response to Zika virus infections, bringing together related central and local departments to prevent Zika virus infection epidemic in Taiwan. To scale up national efforts for Zika virus infection control, Taiwan has four major strategies, including healthcare system preparedness planning, prevention of Zika virus importation, border quarantine, and vector control. Taiwan CDC also issued travel advisory for Zika affected areas and advised pregnant women to postpone their trips to areas with active transmission of Zika virus. Because there are evidences of possible sexual and blood-borne transmissions,[11—13] condom use and deferral of blood product donation for 28 days upon return from areas with active Zika virus transmission has been recommended. To prevent Zika virus from taking root in Taiwan and further control the spread of dengue fever, vector control is of utmost importance. Taiwan CDC continues to disseminate prevention messages to the public and stepping up mosquito breeding site elimination efforts through community education and mobilization.

Besides the first imported case of Zika virus infection in a Thai national detected at the airport in Taiwan on January 10, 2016, thus far, no other cases of Zika virus infection have been identified in Taiwan. In addition, no significant increase in the number of microcephaly or Guillain-Barré Syndrome has been observed. Therefore, we concluded that there have been no autochthonous transmissions of Zika virus infection in Taiwan to date. However, the risk of imported disease rises with time. Current goals are focused on disease surveillance, healthcare system preparedness, border quarantine, and health education. Reducing panic among the people can be achieved by preventing the importation of Zika virus infection.

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